DEPARTMENT OF THE AIR FORCE
59TH MEDICAL WING (AETC)
JOINT BASE SAN ANTONIO - LACKLAND TEXAS

6 APR 2017

MEMORANDUM FOR SGOBS
ATTN: MAJ SUSAN WHITEWAY

FROM: 59 MDW/SGVU

SUBJECT: Professional Presentation Approval

1. Your paper, entitled **Ovarian Sertoli-Leydig Cell Tumor with Elevated Inhibin B as A Cause of Secondary Amenorrhea in Adolescent with Germline DICER1 Mutation** presented at/published to **Journal of Pediatric and Adolescent Gynecology** in accordance with MDWI 41-108, has been approved and assigned local file #**17159.**

2. Pertinent biographic information (name of author(s), title, etc.) has been entered into our computer file. Please advise us (by phone or mail) that your presentation was given. At that time, we will need the date (month, day and year) along with the location of your presentation. It is important to update this information so that we can provide quality support for you, your department, and the Medical Center commander. This information is used to document the scholarly activities of our professional staff and students, which is an essential component of Wilford Hall Ambulatory Surgical Center (WHASC) internship and residency programs.

3. Please know that if you are a Graduate Health Sciences Education student and your department has told you they cannot fund your publication, the 59th Clinical Research Division may pay for your basic journal publishing charges (to include costs for tables and black and white photos). We cannot pay for reprints. If you are a 59 MDW staff member, we can forward your request for funds to the designated Wing POC at the Chief Scientist's Office, Ms. Alice Houy, office phone: 210-292-8029; email address: alice.houy.civ@mail.mil.

4. Congratulations, and thank you for your efforts and time. Your contributions are vital to the medical mission. We look forward to assisting you in your future publication/presentation efforts.

Linda Steel-Goodwin

LINDA STEEL-GOODWIN, Col, USAF, BSC
Director, Clinical Investigations & Research Support

PROCESSING OF PROFESSIONAL MEDICAL RESEARCH/TECHNICAL PUBLICATIONS/PRESENTATIONS

INSTRUCTIONS

USE ONLY THE MOST CURRENT 59 MDW FORM 3039 LOCATED ON AF E-PUBLISHING

1. The author must complete page two of this form:
   a. In Section 2, add the funding source for your study [e.g., 59 MDW CRD Graduate Health Sciences Education (GHSE) (SG5 O&M); SG5 R&D; Tri-Service Nursing Research Program (TSNRP); Defense Medical Research & Development Program (DMRDP); NIH; Congressionally Directed Medical Research Program (CDMRP) ; Grants; etc.]

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2. Print your name, rank/grade, sign and date the form in the author's signature block or use an electronic signature.

3. Attach a copy of the 59 MDW IRB or IACUC approval letter for the research related study. If this is a technical publication/presentation, state the type (e.g. case report, QA/QI study, program evaluation study, informational report/briefing, etc.) in the "Protocol Title" box.

4. Attach a copy of your abstract, paper, poster and other supporting documentation.

5. Save and forward, via email, the processing form and all supporting documentation to your unit commander, program director or immediate supervisor for review/approval.

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11. The Joint Ethics Regulation (JER) DoD 5500.07-R, *Standards of Conduct*, provides standards of ethical conduct for all DoD personnel and their interactions with other non-DoD entities, organizations, societies, conferences, etc. Part of the Form 3039 review and approval process includes a legal ethics review to address any potential conflicts related to DoD personnel participating in non-DoD sponsored conferences, professional meetings, publication/presentation disclosures to domestic and foreign audiences, DoD personnel accepting non-DoD contributions, awards, honoraria, gifts, etc. The specific circumstances for your presentation will determine whether a legal review is necessary. **If you (as the author) or your supervisor check "NO" in block 17 of the Form 3039, your research or technical documents will not be forwarded to the 502 ISG/JAC legal office for an ethics review.** To assist you in making this decision about whether to request a legal review, the following examples are provided as a guideline:

    For presentations before professional societies and like organizations, the 59 MDW Public Affairs Office (PAO) will provide the needed review to ensure proper disclaimers are included and the subject matter of the presentation does not create any cause for DoD concern.

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PROCESSING OF PROFESSIONAL MEDICAL RESEARCH/TECHNICAL PUBLICATIONS/PRESENTATIONS

1. TO: CLINICAL RESEARCH	2. FROM: (Author's Name, Rank, Grade, Office Symbol)	3. GME/GHSE STUDENT:	4. PROTOCOL NUMBER:
	Susan Whiteway, Maj, 0-4, SGOBS	☐ YES ☒ NO	

5. PROTOCOL TITLE: (**NOTE:** For each new release of medical research or technical information as a publication/presentation, a new 59 MDW Form 3039 must be submitted for review and approval.)

6. TITLE OF MATERIAL TO BE PUBLISHED OR PRESENTED:
Ovarian Sertoli-Leydig cell tumor with elevated inhibin B as a cause of secondary amenorrhea in adolescent with germline DICER1 mutation

7. FUNDING RECEIVED FOR THIS STUDY? ☐ YES ☒ NO FUNDING SOURCE:

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Journal of Pediatric and Adolescent Gynecology

☐ 11b. PUBLISHED ABSTRACT (List intended journal.)

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14. 59 MDW PRIMARY POINT OF CONTACT (Last Name, First Name, M.I., email)	15. DUTY PHONE/PAGER NUMBER
Whiteway, Susan L, susan.l.whiteway.mil@mail.mil	210-916-8300/513-9590

16. AUTHORSHIP AND CO-AUTHOR(S) List in the order they will appear in the manuscript.

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17. IS A 502 ISG/JAC ETHICS REVIEW REQUIRED (JER DOD 5500.07-R)? ☐ YES ☒ NO

I CERTIFY ANY HUMAN OR ANIMAL RESEARCH RELATED STUDIES WERE APPROVED AND PERFORMED IN STRICT ACCORDANCE WITH 32 CFR 219, AFMAN 40-401_IP, AND 59 MDWI 41-108. I HAVE READ THE FINAL VERSION OF THE ATTACHED MATERIAL AND CERTIFY THAT IT IS AN ACCURATE MANUSCRIPT FOR PUBLICATION AND/OR PRESENTATION.

18. AUTHOR'S PRINTED NAME, RANK, GRADE	19. AUTHOR'S SIGNATURE	20. DATE
Susan Whiteway, Maj, 0-4	WHITEWAY.SUSAN.L.1146819873	March 24, 2017
21. APPROVING AUTHORITY'S PRINTED NAME, RANK, TITLE	22. APPROVING AUTHORITY'S SIGNATURE	23. DATE
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26. DATE REVIEWED 29 Mar 2017		27. DATE FORWARDED TO 502 ISG/JAC

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29. COMMENTS ☒ APPROVED ☐ DISAPPROVED

The abstract and manuscript are approved.

30. PRINTED NAME, RANK/GRADE, TITLE OF REVIEWER	31. REVIEWER SIGNATURE	32. DATE
Rocky Calcote, PhD, Clinical Research Administrator	CALCOTE.ROCKY.D.1178245844	

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Kevin Iinuma, SSgt/E-5, 59 MDW Public Affairs	IINUMA.KEVIN.MITSUGU.1296227613	March 29, 2017

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Abstract

Background: Although uncommon in children, ovarian tumors can retain endocrine function that disrupts normal feedback mechanisms leading to amenorrhea. Inheritance of germline *DICER1* mutations can lead to increased risk for development of ovarian Sertoli-Leydig cell tumors (SLCT).

Case: We report the case of an adolescent female who developed secondary amenorrhea due to elevated inhibin B levels from an ovarian SLCT.

Summary and Conclusions: Ovarian tumors should be included in the differential diagnosis for pediatric patients presenting with menstrual irregularities. Early evaluation of the hypothalamic-pituitary-ovarian axis is appropriate to include screening of inhibin levels if an ovarian mass is identified. Our case also emphasizes the need for testing of *DICER1* mutations in pediatric patients with ovarian SLCTs.

Ovarian Sertoli-Leydig cell tumor with elevated inhibin B as a cause of secondary amenorrhea in adolescent with germline *DICER1* mutation

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Key Words: Sertoli-Leydig cell tumor, amenorrhea, inhibin B, *DICER1*

Introduction:

The normal menstrual cycle is regulated through a complex and closely coordinated cycle of activating and inhibiting signals that ultimately leads to the release of a mature oocyte. Ovarian tumors can retain endocrine function leading either to androgenic or estrogenic manifestations such as isosexual precocious puberty, virilization from hyperandrogenism, or secondary amenorrhea from disrupted hormonal pathways. Here we present the case of an adolescent female who developed secondary amenorrhea due to elevated inhibin B levels from an ovarian Sertoli-Leydig cell tumor (SLCT). After tumor recurrence, the patient was found to harbor a germline loss of function *DICER1* mutation. This gene encodes an endonuclease that is critical for microRNA processing and affected individuals are at risk for developing rare tumors such as a SLCT. Identification of a *DICER1* mutation is clinically relevant due to the potential for a synchronous *DICER1*-related disorder and increased tumor risk in affected family members.

Case:

The patient presented at age 14 years to her primary care provider for evaluation of irregular menstrual periods. She underwent menarche at age ten with menstrual cycles occurring at regular 28 day intervals with five days of menstrual flow. Three months prior to presentation, her menses stopped. She also reported intermittent, sharp, right-sided pelvic pain but denied sexual activity, recent weight change, hot flashes, voice changes, or increased hair growth.

Her past medical history was significant for a right ovarian SLCT, found at age eight years which presented with ovarian torsion. The tumor was 12 cm in size, para-ovarian in location, with retiform histology, and was removed via cystectomy to ensure ovarian

preservation during exploratory laparotomy. She was dispositioned for ultrasound surveillance and had been followed conservatively for three years.

At current evaluation, she was at the 60th percentile for height and weight with no increased growth velocity. She was Tanner stage V for sexual maturity rating and physical exam was without evidence of a palpable abdominal mass, acne, hirsutism, or clitoromegaly. Screening pelvic ultrasound and confirmatory magnetic resonance imaging (MRI) showed a 5 cm x 4.1 cm complex left ovarian mass with solid and cystic components. Laboratory evaluation demonstrated elevated inhibin B level 286 pg/mL (<177 pg/mL for Tanner Stage V female) and luteinizing hormone (LH) 40.2 mIU/mL (2.4 mIU/mL-12.6 mIU/mL in follicular phase) with negative beta human chorionic gonadotropin (beta-HCG), and normal testosterone, dehydroepiandrosterone sulfate (DHEA-S), estradiol, cancer antigen (CA)-125, follicle stimulating hormone (FSH), inhibin A, and thyroid hormone levels.

She underwent an uncomplicated left salpingo-oophorectomy, omental sampling, right ovarian biopsy, and peritoneal washings. Pathology was consistent with a moderately differentiated SLCT, without heterologous elements. The ovarian capsule was intact; however the peritoneal washings were positive for involvement of a SLCT. Immunohistochemical staining of the neoplastic cells were positive for alpha-inhibin. There was no omental involvement and two omental lymph nodes were negative for metastatic involvement. The tumor was International Federation of Obstetrics and Gynecology (FIGO) stage 1C due to involved peritoneal washings at the pelvic entry. The patient resumed her regular menses 21 days after surgical resection and her hormone levels normalized with inhibin B 7.71 pg/mL and LH 12.4 mIU/mL. In light of her Stage IC disease, she was treated with 4 cycles of bleomycin, etoposide, and cisplatin chemotherapy without complication. At completion of therapy she was without

evidence of disease based on normal serum inhibin B levels and negative MRI findings. With close follow up monitoring of inhibin B levels and pelvic ultrasound, initially at an every 3 month interval and now at 6 month intervals, our patient continues in remission with no concern for disease recurrence at 23 months off therapy.

Given that our patient was diagnosed with an ovarian SLCT initially at a young age with late recurrence, she underwent a commercially available gene sequence analysis of *DICER1* that showed the pathogenic mutation c.1839delA at exon 10, predicted to be an alternate stop codon. As there are no formal guidelines for patients with germline *DICER1*-related disorders, we pursued screening tests in conjunction with published recommendations. Our patient had chest computed tomography (CT) that was negative for pulmonary cysts seen in pleuropulmonary blastoma (PPB), pelvic MRI for her ovarian tumor was negative for renal pathology, and she had no thyroid nodules on physical exam. Apart from her pelvic imaging for SLCT surveillance, her *DICER1* follow up will consist of annual physical exams, targeted review of systems, and imaging only to examine areas of concern if found on exam.

Summary and Conclusion:

The absence of normal menstruation, defined as primary or secondary amenorrhea, can arise from a variety of conditions. In the adolescent patient, most cases of secondary amenorrhea can be attributed to pregnancy, polycystic ovarian syndrome, hyperprolactinemia, hypothalamic amenorrhea, primary ovarian insufficiency, or an ovarian tumor.[1] Initial evaluation for a patient with secondary amenorrhea involves a thorough history and physical exam to look for progression of height, weight, and Tanner staging. Presence of acne, hirsutism, and virilization would suggest an androgenic state. Laboratory evaluation includes serum beta-HCG, LH, FSH, prolactin level, and thyroid stimulating hormone. Diagnostic imaging with pelvic

ultrasonography can confirm the presence of a uterus, possible outflow tract abnormalities, or an ovarian tumor.[1]

Ovarian tumors are extremely rare in young children, accounting for only 1% of all pediatric tumors.[2] Ovarian SLCTs belong to a heterogeneous group of tumors that arise from the non-germ cell component of the ovary. These tumors typically present in the first two to three decades of life.[3] They are often unilateral, large (10-15cm), and present with abdominal pain, distension, and can lead to torsion. Histologic subtypes include well, intermediate, and poorly differentiated as well as retiform.[4]

Unlike other ovarian tumors such as germ cell or epithelial cancers, SLCT often present with evidence of hormonal dysfunction such as precocious puberty, amenorrhea, or hyperandrogenism with hirsutism and virilization.[3] Laboratory findings may include elevation of hormonal markers such as inhibins A or B, estrogen, testosterone, or AFP which can be increased in the retiform subtype.[5] Due to rarity of this tumor, no standard treatment approach had been identified. For localized FIGO Stage 1a disease in children and adolescents, most tumors can be treated with surgery alone to include fertility-sparing resection of affected ovary and fallopian tube instead of total hysterectomy and bilateral salpingo-oophorectomy often offered to women beyond reproductive age.[3] For higher staged tumors, a cisplatin based regimen should be recommended as adjuvant therapy.[4]

Our patient presented with clinical findings of secondary amenorrhea and abdominal pain. Evaluation into potential etiologies led to identification of an elevated LH level in the presence of normal estradiol and FSH levels. With an ovarian mass seen on pelvic imaging, serum tumor markers were drawn and showed an elevated inhibin B level with normal inhibin A, testosterone, DHEA-S, and CA-125 levels. This unusual laboratory pattern has been previously

described in adult patients with an ovarian fibrothecoma and a leiomyoma but not previously in a patient with SLCT.[6]

In the menstrual cycle, early in the follicular phase, gonadotropin releasing hormone (GnRH) pulses and a small surge of FSH initiates recruitment of the next cohort of follicles. With progression through the follicular phase, the modest increase in FSH stimulates folliculogenesis and estradiol production. Levels of inhibin B, secreted by the granulosa cells of developing follicles, rise and function to regulate FSH secretion through negative feedback inhibition.[6] It is hypothesized that autonomous inhibin B production from these tumors results in amenorrhea from complete inhibition of follicular recruitment due to chronic FSH suppression. In an attempt to overcome FSH suppression, the hypothalamus has an exaggerated GnRH release which leads to disproportionately elevated release of LH.[6] (Figure 1). In our patient, after complete tumor resection, normal physiologic feedback patterns were reestablished. Clinically, there was evidence of resumed follicular recruitment with an increase in estradiol, decrease in LH and inhibin B levels, and resumption of menses.

Recent reports have identified an association between germline *DICER1* mutations and SLCTs[3]. *DICER1* encodes an enzyme required for the production of mature microRNAs, which are important regulators of gene expression and critical in normal organ development.[7] Germline *DICER1* mutations were first identified in cases of PPB, the most common lung tumor of infancy and early childhood.[8] The *DICER1*-related disorders have expanded to include other ovarian sex cord-stromal tumors (juvenile granulosa cell tumor and gynandroblastoma), cystic nephroma, and thyroid gland neoplasia. Less common tumors include ciliary body medullopithelioma, botryoid-type embryonal rhabdomyosarcoma, nasal chondromesenchymal hamartoma, pituitary blastoma, and pinealblastoma.[5] Patients with germline *DICER1* mutations and ovarian SLCTs

have been reported to present at a younger age, have a higher incidence of bilateral disease, and are at risk of developing a late contralateral, metachronous ovarian tumor after the general risk period for recurrence.[3] *DICER1* mutations are inherited in an autosomal dominant manner and although penetrance is suspected to be low, identification of a germline *DICER1* affected patient is recommended as it may have screening implications for both the patient and family members.[5]

Given the rarity of this condition, no formal guidelines regarding initial screening evaluations or surveillance of persons with a germline *DICER1* pathogenic variant have been established. However, based on data from the International PPB registry which includes more than 500 persons affected, screening recommendations include an annual physical exam with special attention to thyroid gland, targeted review of systems, and baseline screening imaging of chest (CT) and kidneys (ultrasound) that is tailored to age at diagnosis and presence of any suspicious clinical findings.[5]

This case highlights the importance of recognizing the potential for ovarian tumors to affect the menstrual cycle in pediatric and adolescent patients. We emphasize early evaluation of the hypothalamic-pituitary-ovarian axis and inhibin B levels if an ovarian tumor is identified to screen for these rare patients and advocate for *DICER1* testing in affected pediatric patients to establish need for surveillance of possible synchronous tumors, risk for tumor recurrence, and to identify affected family members.

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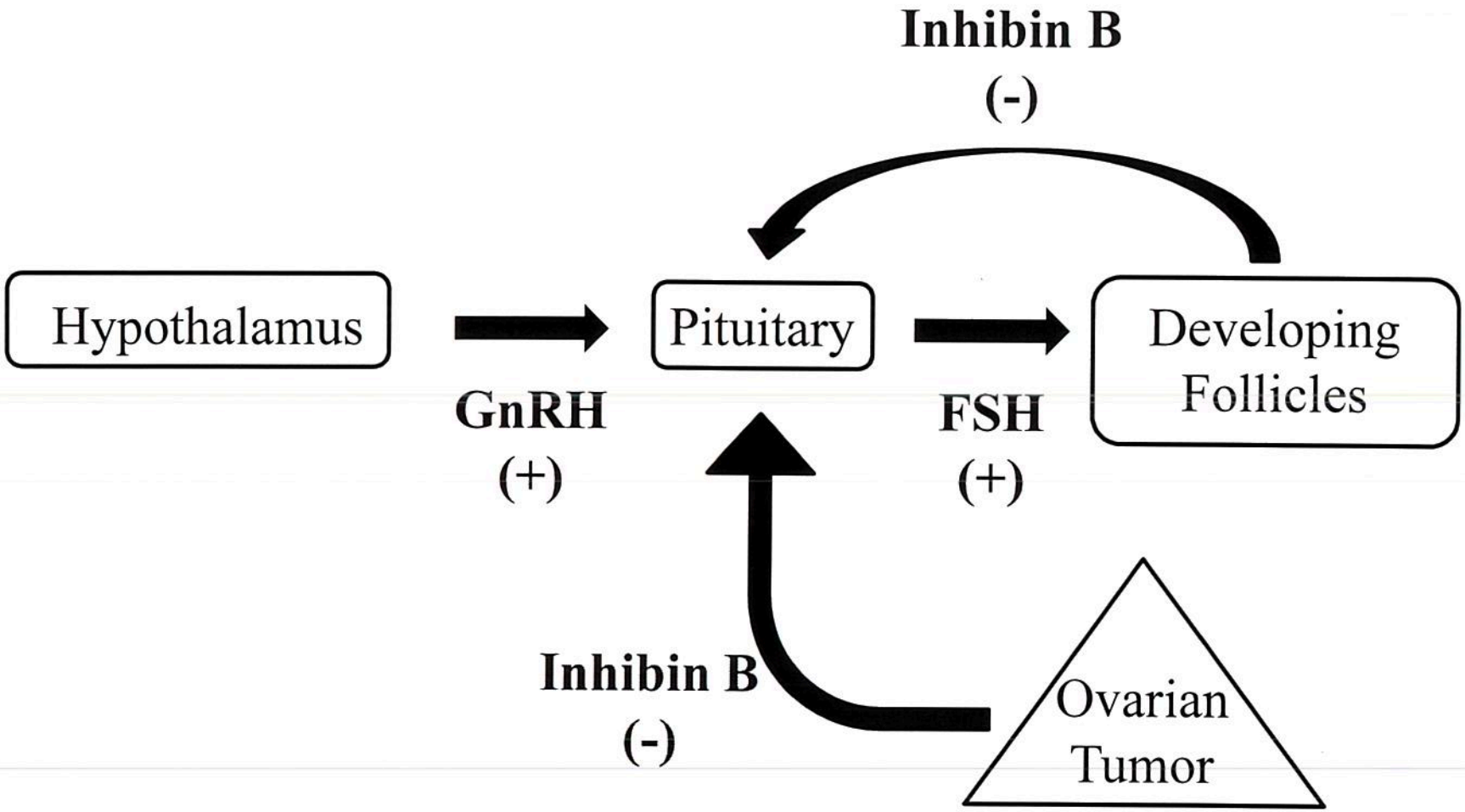
Figure 1: In early follicular phase, hypothalamic GnRH pulses lead to FSH release from the pituitary, initiating folliculogenesis. Inhibins B levels, from developing follicles, increase and through feedback inhibition, suppress FSH levels. Autonomous secretion of inhibin B by ovarian tumors interrupts this feedback loop leading to FSH suppression, absent folliculogenesis, and amenorrhea.


Inhibin B
(-)
Hypothalamus
GnRH
(+)
Pituitary
FSH
(+)
Developing
Follicles
Inhibin B
(-)
Ovarian
Tumor